Approach to Venous Thromboembolism

Ponlapat Rojnuckarin, MD PhD
Chulalongkorn University
Venous Thromboembolism

Deep vein thrombosis (DVT)

Calf vein → Proximal vein (Above knee) → Embolism
Inherited hypercoagulability (Thrombophilia)

- Protein S deficiency
- Protein C deficiency
- Antithrombin deficiency
- Activated protein C resistance
- Prothrombin mutation G20210A
- Dysfibrinogenemia
- Others……..
Acquired hypercoagulable states

- Malignancy (20-40%)
- Antiphospholipid antibody (10.4%)
- Myeloproliferative diseases
- Paroxysmal nocturnal hemoglobinuria
- Nephrotic syndrome
- Heparin-induced thrombocytopenia

Genetic/acquired: Mixed or unknown

Hyperhomocysteinemia
High levels of clotting factors
Predisposing factors

- Age
- Trauma
- Immobilization
- postoperative state
- Intravenous catheter
- Air Travel
- Estrogen (3x)
- Pregnancy (4x)
Multifactorial DVT

Examples
- Old age
- Cancer
- Surgery
- Hereditary thrombophilia
- Oral contraception
Venous Thromboembolism (VTE = DVT + PE)

Pulmonary embolism (PE): 20% sudden death before diagnosis

Clinical suspicion: Immediate anticoagulant while waiting for investigation
Pulmonary embolism (PE)

- Unexplained dyspnea
- Tachypnea
- Tachycardia
- Pleuritic chest pain (Pulmonary infarction)
- Dizziness or coma
- Death
Chronic Complications of VTE

56% Post-thrombotic syndrome
Valve damages ± Persistent thrombus
Pain, swelling, skin changes, ulcer
No effective treatment

Chronic Pulmonary Hypertension
Persistent thrombus
Chronic dyspnea
Rx surgery to removal clot

Venous ulcer 10%
Deep vein thrombosis

Unilateral Swelling
Pitting edema
Warm Erythema
Tenderness of veins
Pain on dorsiflexion (Homan’s sign)
May be asymptomatic
Ultrasonography (Non Compressible)
Loss of respiratory phasic waves

NORMAL

PROXIMAL OBSTRUCTION

e.g. Iliac vein thrombosis
Venous Anatomy

SFV is a deep vein.

Popliteal v. is a proximal vein.

Sometimes, distal veins cannot be seen: needs repeat at 1 wk, if still suspicion
A 62-yr-old woman with HT, DLP come to OPD with leg swelling Rt > Lt 1 wk

- No other illnesses
- Pitting edema Rt > Lt
- On Amlodipine
- D dimer 582 µg/L
  (Normal < 500 µg/L)
- Will you request Doppler US?
Current VTE Diagnostic Algorithm

1. Suspected DVT or PE
   - Clinical pre-test probability
     - Low or intermediate
       - D-dimer
         - Normal
           - Diagnosis excluded
         - Elevated
           - Compression ultrasound or CT pulmonary angiogram
             - Negative
               - Diagnosis excluded
             - Positive
               - Diagnosis established
     - High
       - Compression ultrasound or CT pulmonary angiogram
         - Negative
           - Diagnosis excluded
         - Positive
           - Diagnosis established
False-positive D dimer
Less helpful in these conditions

**TABLE 2** Patient Characteristics and Disorders Associated With Increased D-Dimer Levels

- Venous or arterial thrombosis
- Disseminated intravascular coagulation
- Advanced age
- Recent surgery or trauma
- Cancer
- Pregnancy or puerperium
- Infection
- Chronic inflammation
- Liver disease
- Renal disease
- Thrombolytic therapy

J Am Coll Cardiol 2017; 70: 2411
Age-adjusted D dimer

- D dimer is increasing with age.
- Patients ≤ 50 yrs old: Cutoff < 500 μg/L
- Patients > 50 yrs old: Cutoff = Age x 10 μg/L
- More studies in PE
- False positive rate
  - Decrease 5-6%
  - Decrease 10-20% in patients > 70 yrs old

J Thromb Haemost 2018; 16: 866
Ann Intern Med 2016; 165: 253
D-Dimer in VTE Diagnosis

- Not helpful for high pre-test probability
- Diagnosis scheme allows up to 3% misdiagnosis.
- Less helpful for recurrent DVT, Cancer, Post-operation, inpatients
- All D-Dimer tests are **NOT** the same! Literature review is important.
- Age-adjusted or Clinically-adjusted cutoffs can be used.
A 62-yr-old woman with HT, DLP come to OPD with leg swelling Rt > Lt 1 wk

- No other illnesses
- Pitting edema Rt > Lt
- On Amlodipine
- D dimer 582 µg/L
  (Normal < 500 µg/L)
- No Doppler US

Age-adjusted D dimer < 620 µg/L
Clinically-adjusted D dimer < 1000 µg/L
A 80-yr-old woman presents with left leg edema BW 40 kg Cr 1.0 mg/dL

Compression of vein

- A. Enoxaparin 40 mg q 12 h
- B. Rivaroxaban 15 mg bid
- C. Tinzaparin 175 U/kg/d
- D. Warfarin 5 mg/d

CrCl 28 ml/min

Adjusted dose enoxaparin
Tinzaparin (CrCl 20 ml/min)
Unfractionated heparin
Apixaban 10 mg bid (CrCl 25 ml/min)
LMWH

- Compared with UFH: Less Heparin Induced Thrombocytopenia (HIT) and Less osteoporosis in long-term use
- Cannot be reversed completely by protamine
- Reduce doses if CrCl ≤ 30 ml/min
  - Monitoring: anti Xa activity (4 hr after last dose)
    Therapeutic range: 0.6-1 IU/ml (bid dose)
    1-2 IU/ml (od dose)
  - Use standard heparin
Fatal retroperitoneal bleeding in renal failure

Case report
Old female patient
Cr 1.2 mg%
Calculated CrCl < 30 ml/min
Enoxaparin 1 mg/kg/d

Pharmacotherapy. 2005;25:769-72

eCrCl = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{72 \times \text{Creatinine}_{serum} (mg/dL)} \times 0.85 \text{ if female}
Warfarin

- Start with heparin until INR 2.0-3.0
- At least 4-5 days overlap
- First few days
  - May be hypercoagulable due to low protein C and protein S
  - Prolonged PT due to low factor VII
- Anticoagulant property: Low prothrombin (at least 4 days)
- Many food/drug/supplements interactions
Direct oral anticoagulants (DOACs)

- Overcome current LMWH and warfarin limitations
- Warfarin limitations
  - Slow onset/offset
  - Monitoring
  - Numerous drug/food interactions
- LMWH limitations
  - Injections
Targets of oral anticoagulants

DOACs  
Direct oral anticoagulants

NOACs  
Novel oral anticoagulants  
New oral anticoagulants  
Non vitamin K antagonist oral anticoagulants

Nat Rev Cardiol 2014; 11: 290
DOACs vs. Warfarin in VTE Rx

Meta-analysis (N 24 455)

- Recurrent VTE 0.88 [0.74-1.05]
- Fatal PE 1.02 [0.39-5.96]
- Total mortality 0.97 [0.83-1.14]
- Major bleeding 0.60 [0.41-0.88]

Number needed to treat (NNT) = 149

- Fatal Bleeding 0.36 [0.15-0.87]

Number needed to treat (NNT) = 1111

## DOAC comparison

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Thrombin</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>7%</td>
<td>60-80%</td>
<td>80%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>HL</strong></td>
<td>12-17 h</td>
<td>7-11 h</td>
<td>12 h</td>
<td>9-11 h</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>80% renal</td>
<td>60% renal</td>
<td>25% renal*</td>
<td>35% renal</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>conjugation</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>minor</td>
</tr>
<tr>
<td><strong>p-Gp interaction</strong></td>
<td>yes</td>
<td>yes</td>
<td>minimal</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Antidotes</strong></td>
<td>Idarucizumab</td>
<td>Andexanet α or 4F-PCC (Not available in Thailand)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CrCl limit of 25 ml/min

J Thromb Thrombolysis 2011; 31:310, Nat Rev Cardiol 2012;
## DOAC Doses in VTE Treatment

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial phase</strong></td>
<td>Parenteral</td>
<td>15 mg bid</td>
<td>10 mg bid</td>
<td>Parenteral</td>
</tr>
<tr>
<td></td>
<td>5-10 d</td>
<td>3 weeks</td>
<td>1 week</td>
<td>5-10 d</td>
</tr>
<tr>
<td><strong>Long term phase</strong></td>
<td>150 mg bid</td>
<td>20 mg OD</td>
<td>5 mg bid</td>
<td>60 mg OD</td>
</tr>
<tr>
<td><strong>Reduced doses</strong></td>
<td>CrCl 15-30</td>
<td>‘AF ONLY’</td>
<td>‘AF ONLY’</td>
<td>CrCl 30-50</td>
</tr>
<tr>
<td></td>
<td>75 mg bid</td>
<td>CrCl 15-50</td>
<td>CrCl 30-50</td>
<td>BW ≤ 60 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mg OD</td>
<td>Age &gt; 80 y, BW &lt; 60 kg, Cr &gt; 1.5 mg/dL</td>
<td>P-GP Inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30 mg OD</td>
</tr>
</tbody>
</table>

References:

- J Thromb Thrombolysis 2011; 31:310, Nat Rev Cardiol 2012;
A 81-yr-old woman with unprovoked DVT Rx with LMWH/VKA for 6 months

INR is labile.
PH: HT and DM
No Major bleeding.
Stop warfarin 4 weeks
D dimer 1250 µg/L
Should she stop warfarin?
VTE treatment scheme

- **Initial Phase**: First 1-3 wk
- **Long-term Phase**: 7 day – 3 to 6 months
- **Extended Phase**: After 3 to 6 months

**Phase 1** (First week) High Intensity to prevent fatal PE
**Phase 2** (until 3-6 months*) Prevent recurrence
**Phase 3** (after 3-6 months*): Weigh risks of Recurrence vs. Bleeding for start/stop and intensity

*3 m for provoked VTE
6 m for unprovoked VTE

Modified from ACCP recommendation. Chest 2012; 141: e419s
VTE will recur after stopping anticoagulants.

545 patients up-to 10 years

Provoking factor is the major determinant for VTE recurrences

Major surgery or Trauma
Incurable Cancer
Bed-ridden
Strong thrombophilia

Proved VTE
Transient risk factor

Unprovoked VTE

Provoked VTE
Persistent risk factor

Transient provoking factor
No provoking factor
Persistent provoking factor

Risk of recurrence

< 5% in 1 yr
<15% in 5 yr
Defined as acceptable risk

J Thromb Haemost 2016; 14: 1480
J Thromb Haemost 2010; 8: 2313
# Risk scores for recurrence in first unprovoked VTE

<table>
<thead>
<tr>
<th></th>
<th>HERDOO2</th>
<th>Vienna</th>
<th>DASH</th>
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</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>646</td>
<td>929</td>
<td>1818</td>
</tr>
<tr>
<td>Exclusion</td>
<td>LA, PC, PS, AT deficiency</td>
<td>LA, PC, PS, AT def, hormone</td>
<td>APS, AT deficiency</td>
</tr>
<tr>
<td>D dimer</td>
<td>$\geq 250$ ug/L (+1)</td>
<td>Levels</td>
<td>$\geq 500$ ug/L (+2)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female only</td>
<td>Male</td>
<td>Male (+1)</td>
</tr>
<tr>
<td>Age</td>
<td>$\geq 65$ Yr (+1)</td>
<td>$\leq 50$ yr (+1)</td>
<td></td>
</tr>
<tr>
<td>Other risk factors</td>
<td>BMI $\geq 30$ kg/m²(+1) PTS symptoms (+1)</td>
<td>Proximal DVT or PE</td>
<td>Hormone (-2)</td>
</tr>
<tr>
<td>Acceptable risk</td>
<td>&lt; 2</td>
<td>Program will Calculate the risk</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

BMJ Open 2016; 6: e011190
VTE recurrence in Thai patients at KCMH
After stopping anticoagulant (N = 144)
D-dimer and VTE recurrences in Thai patients

PTS before recurrences (25% vs. 5.9%, p = 0.018)

Kijrattanakul et al
JTH 2015; 13 (S2):726
To Continue or Stop Anticoagulant

- Thrombosis vs. Bleeding risk for each patient
- Severity of the first episode e.g. massive PE
- Patient values e.g. 30% DVT vs. 1% CNS bleeding
- Patient preferences/lifestyle e.g. Long-term medication, Risk of trauma, Living far from health care facilities
Both Rivaroxaban Doses Reduced Recurrent VTE Rates and Similar Risk of Bleeding Compared with ASA

**Efficacy***

![](image1.png)

**Major bleeding***

![](image2.png)

*Intention-to-treat analysis; †safety analysis; ‡no events after Day 360 up to Day 480

Apixaban extension therapy
After 6-12 months of anticoagulants

Recurrent VTE

Major and Clinically relevant
Non Major Bleeding

## Safety of low dose DOACs

<table>
<thead>
<tr>
<th>Trials</th>
<th>Settings</th>
<th>N</th>
<th>Intervention</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adopt</td>
<td>VTE prophylaxis in Medical patients</td>
<td>6528</td>
<td>Apixaban 2.5 mg bid 30d Enoxaparin 40 mg od 6-14 d</td>
<td>2.58 (1.02-7.24)</td>
</tr>
<tr>
<td>Megellan</td>
<td>VTE prophylaxis in Medical patients</td>
<td>8101</td>
<td>Rivaroxaban 10 mg od 35d Enoxaparin 40 mg od 35 d</td>
<td>2.9 (1.6-5.15)</td>
</tr>
<tr>
<td>Mariner</td>
<td>VTE prophylaxis in Medical patients</td>
<td>11024</td>
<td>Rivaroxaban 10/7.5 mg od 45 d vs. Placebo 45 d</td>
<td>1.88 (0.84-4.23)</td>
</tr>
<tr>
<td>Compass</td>
<td>Stable Coronary disease</td>
<td>27395</td>
<td>Rivaroxaban 5 mg bid vs. ASA</td>
<td>1.51 (1.25-1.84)</td>
</tr>
</tbody>
</table>
A 81-yr-old woman with unprovoked DVT Rx with LMWH/VKA for 6 months

High risk of recurrence
High risk of bleeding from warfarin
Low dose DOACs appear to be safer choice but COST is the major concern.
ASA, Sulodexide or Warfarin (INR1.5-2) may be considered.

If the initial episode was massive PE, extended therapy is recommended.
A 59-yr-old female with CA cervix
On radiotherapy with Rt leg edema

Rt Common iliac vein thrombosis
What is your treatment?
1. LMWH
2. LWMH/VKA
3. DOACs
LMWH vs. Warfarin and recurrent symptomatic DVT in cancer

DVT Recurrence 17% vs. 9% in 3 m

TTR 46%

Guidelines for cancer VTE

- ACCP 2016 (Chest 2016; 149: 315)
  - LMWH for 3 months
- ASCO 2014 (JCO2015; 33: 654)
  - LMWH for 6 months
- British guideline (BJH 2015;170:640)
  - LMWH for 6 months
- Canadian guideline (Curr Oncol 2015; 22; 144)
  - LMWH for > 3 months
- Thai Society of Hematology (Jan 2018)
  - LMWH for 3-6 months
Edoxaban 60 mg /d (after LMWH x 5d) is not inferior to Dalteparin in Cancer VTE.

Rivaroxaban vs. Dalteparin in Cancer VTE

CRNMB HR 3.76 (1.63-8.69)

DOAC: More bleeding in GI cancer

Select D trial J Clin Oncol 2018; 36: 2017
DOACs in cancer VTE

- More convenient and less expensive than LMWH with similar efficacy.
- More bleeding in GI cancer
- Some interactions with anticancer agents (CYP3A4 or P-glycoprotein)
- Not reimbursable (Non-ED)
A 59-yr-old female with CA cervix
On radiotherapy with Rt leg edema

Rt Common iliac vein thrombosis in non-GI cancer

Treatment
1. DOACs
2. LMWH
3. LMWH/VKA*

*Low-risk cancer patients who cannot use LMWH or DOACs
Risk Factors in Cancer patients

<table>
<thead>
<tr>
<th>General factors</th>
<th>Cancer-specific factors</th>
<th>Treatment-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Site of cancer: brain, pancreas, kidney, stomach, lung, bladder, gynecologic, hematologic malignancies</td>
<td>Surgery</td>
</tr>
<tr>
<td>Gender</td>
<td>Stage of cancer: advanced stage</td>
<td>Chemo- and hormone-therapy</td>
</tr>
<tr>
<td>Immobility</td>
<td>Initial period of diagnosis</td>
<td>Anti-angiogenic therapy</td>
</tr>
<tr>
<td>Previous VTE</td>
<td></td>
<td>Erythropoiesis stimulating agents</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td>Blood transfusions</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>Central venous lines</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
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</tr>
</tbody>
</table>

Breast and **prostate CA** have low-risk.
Summary

- Age-adjusted D dimer cutoff to exclude VTE
- Treatment of VTE
  - LMWH: Beware renal dysfunction
  - Warfarin: Patient education
  - DOACs: Renal function/ few drug interactions
- Duration of anticoagulants: VTE vs. bleeding risk
- Cancer-associated VTE: Cancer site, Patient preference, Reimbursement